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Changes in obesity status and lung function decline in a general population sample

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Summary
Aim of this paper was to evaluate the effects of changes in obesity status on lung function decline over an 8-year follow-up.
Adults over 24 years ($n = 1212$) from the general population, who participated in both Po River Delta first (PD1, 1980–1982) and second (PD2, 1988–1991) epidemiological surveys, were stratified as "never obese" (BMI $< 30\,Kg/m^2$ at both PD1 and PD2), "becoming obese" (BMI $< 30\,Kg/m^2$ at PD1 and $\geqslant 30\,Kg/m^2$ at PD2), "always obese" (BMI $\geqslant 30\,Kg/m^2$ at both PD1 and PD2), and "becoming non-obese" (BMI $\geqslant 30\,Kg/m^2$ at PD1 and $< 30\,Kg/m^2$ at PD2). Linear regression models for changes in FEV_1, FVC, and VC (computed as absolute differences between the values at PD2 and those at PD1) with longitudinal categories of obesity, gender, age, and baseline smoking habits as covariates were applied.
The "becoming obese" and "always obese" categories had a significantly greater decline of lung function than "never obese" group; in the "always obese" group, this was true for vital capacities but not FEV_1. Conversely, in the "becoming non-obese" group lung function was at PD2 improved with respect to PD1. Compared with "Never obese" the mean increase in lung function was of 93, 180, and 48 mL for FEV_1, FVC, and VC, respectively.
In this general population sample, remaining or becoming obese increases the decline in lung function over 8 years, while becoming non-obese decreases it.

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Introduction

Obesity is becoming a social and economical problem in the Western World for the numerous respiratory, cardiovascular, and metabolic diseases associated with the increase in body mass.[1,2] Whereas most of the organs or systems of the body slowly react to obesity, the respiratory system quickly adapts by reducing lung volumes and airway caliber.[3–5] As a result, gas exchange worsens,[6] and dynamic compression of the airways downstream from the flow limiting segments occurs,[7] thus explaining symptoms and exercise limitation complained by obese individuals even when their spirometry is still normal or near normal.

Few longitudinal studies have consistently shown that obesity is associated with higher lung function decline.[8–12] Thus, obesity may alter lung function not only by reducing lung volume and airway caliber but also by accelerating the decline in lung function. However, to our knowledge, scanty information is available about the effects of changes in obesity status on lung function decline. The availability of existing longitudinal data from an epidemiological population-based study carried out in 1980s gave us the opportunity to explore this possible association of current respiratory interest.

This study aimed to evaluate in a general population whether changes in obesity status may accelerate or slow down the decline in lung function over an 8-year follow-up.

Material and methods

Study subjects

The present study was performed on 1212 subjects who participated in both the first (PD1) and second (PD2) epidemiological surveys carried out in 1980–1982 and 1988–1991, respectively, on the general population living in the rural area of Po River Delta in Italy. Details of the study design and results of PD study have been previously published.[13–15] Only subjects aged over 24 years at baseline and with complete questionnaire follow-up were included. Study subjects provided verbal informed consent to voluntarily participate in both PD1 and PD2 epidemiological (non-pharmaceutical) surveys. Italian law did not request the approval of Ethical Committee at the time of the field surveys.

Lung function measurements

At both surveys, the same instrument was used for lung function measurements (Fleish no. 3 pneumotachograph, Pulmonary System 47804/S, Hewlett-Packard, Waltham, Massachusetts, USA). The pneumotachograph was heated at 37 °C, and volumes reported in liters at BTPS. Volume calibration was performed daily using a standard 3 L calibrated syringe. The protocol for lung function measurements fulfilled the American Thoracic Society (ATS) recommendations[16] at both surveys, with the exception of the criterion for the end-point of the forced vital capacity (FVC) maneuver[17] (e.g., for FVC maneuvers with an expiration time <16 s, the end-point occurred either at the last flow sample before an inspiratory volume >250 mL or at the last flow sample before a 2 s interval where each flow value was <15 mL/s; the ATS algorithm instead determined the end-point when the average flow during a 0.5 s interval was less than 50 mL/s). Up to eight forced expiratory maneuvers were performed to obtain at least three acceptable spirograms. The two largest FVC and forced expiratory volume in 1 s (FEV_1) values from all acceptable maneuvers had to be within 5% from each other. The largest FVC and FEV_1 were selected regardless of the maneuver. At least two attempts were repeated to obtain a satisfactory slow vital capacity (VC) and the largest value was retained for statistical analysis. Percent predicted values for FEV_1, FVC, and VC were computed according to reference equations derived within PD1 normals.[13]

Variables of interest

The body mass index (BMI) was computed as the ratio of body weight in kilograms to squared-height in meters. On the basis of BMI variations in over time, subjects were stratified into four categories:

- "never obese" (NO), BMI <30 Kg/m^2 at both PD1 and PD2;
- "becoming obese" (BO), BMI <30 Kg/m^2 at PD1 and $\geqslant 30$ Kg/m^2 at PD2;
- "always obese" (AO), BMI $\geqslant 30$ Kg/m^2 at both PD1 and PD2;
- "becoming non-obese" (BNO), BMI $\geqslant 30$ Kg/m^2 at PD1 and <30 Kg/m^2 at PD2.

Height (in centimeters) and weight (in kilograms) were measured in standing position without shoes in subjects wearing clothes. Age at last birthday was recorded. Subjects were defined as "current smokers", "ex-smokers", and "never smokers" on the basis of smoking habit as reported at PD1.

For each subject, longitudinal variation in FEV_1, FVC, and VC was computed as the difference between measurements taken at PD2 and at PD1. Throughout the paper we refer to the variations as ΔFEV_1, ΔFVC, and ΔVC.

Statistical analysis

The distributions of the variables were compared across categories of obesity, separately by gender. *P* values for the differences among categories were obtained by non-parametric Kruskal–Wallis test. *P* values less than 5% were considered statistically significant.

Linear regression models were applied to estimate mean ΔFEV_1, ΔFVC, and ΔVC as functions of obesity categories (4-level categorical variable, reference category NO), gender (binary, reference category females), smoking habit (3-level, reference category never smokers), and age at baseline (continuous, in years). The linearity assumption for the relationship between age and the conditional mean of the outcome variables were tested by means of indicator variables for the quartiles of age. *P* values were calculated by Wald test. Pairwise interactions among covariates were not statistically significant.

Results

Baseline characteristics of the study subjects are reported in Table 1. In both genders: NO had significant lower mean age; AO had significantly higher mean BMI than BNO and, by selection criteria, than BO and NO; mean absolute and percent predicted values of FEV_1, FVC, and VC were the lowest in BNO and the largest in NO and BO. Furthermore, there were statistically significant differences for absolute values across groups in both genders, and for percent predicted values of FVC and VC in females.

Mean absolute differences between values at PD2 and PD1 are reported in Table 2, where negative values of ΔFEV_1, ΔFVC, and ΔVC denote decrease in lung function. The mean increase of weight in BO was around 9 Kg in both genders; the mean decrease of weight in BNO was about 9 Kg in males and 10 Kg in females. Accordingly, BMI increased in BO by about 4 Kg/m^2 in both genders while decreased in BNO by about 3 Kg/m^2 in males and 4 Kg/m^2 in females. While mean decline in FEV_1 for males was 29 mL in BO and 16 mL in AO, it was only 2 mL in BNO. Corresponding figures for females were 30, 23, and 16 mL. Mean decline in FVC for males was 28 mL in BO and 21 mL AO, while a mean increase of 4 mL in FVC over time was observed in BNO. Similar values were observed for VC in males. In females, mean decline of FVC and VC in BO and AO was 27 mL on average. In BNO females, a mean decline of 3 and 16 mL for FVC and VC, respectively, was observed. In both genders, ΔFEV_1, ΔFVC, and ΔVC were statistically different across groups, with BNO showing the lowest mean values; in BNO males, FVC and VC on average increased at follow-up.

Table 3 show the mean ΔFEV_1, ΔFVC, and ΔVC values as coefficients of linear regression models in longitudinal categories of obesity adjusted for baseline gender, age, and smoking habit. With respect to the reference category (NO), BO had a greater and statistically significant decline in lung function, which was of 111,122, and 155 mL for FEV_1, FVC, and VC, respectively. The corresponding figures in AO were 9, 65, and 109 mL, and a statistically significant difference was observed only for FVC and VC. In contrast, BNO yielded positive coefficients for the changes of all three spirometric parameters (statistically significant for ΔFEV_1 and ΔFVC), thus suggesting a reduced lung function decline. Compared with NO, the mean increase in lung function was of 93, 180, and 48 mL for FEV_1, FVC, and VC, respectively. Estimated coefficients of ΔFEV_1, ΔFVC, and ΔVC were always significantly different ($P<0.05$) among the longitudinal categories of obesity, with the exception of ΔFVC and ΔVC between BO and AO. Age coefficient was always negative and statistically significant, due to the natural decline of lung function with age. The decrease in FEV_1 was slightly but significantly greater in women than men. The decrease in FEV_1, FVC, and VC was significantly greater in smokers than in never smokers. Interestingly, the ex-smokers showed a positive ΔFEV_1 coefficient, thus suggesting a relative improvement in lung function over time. The larger decline of the spirometric parameters over time in BO and AO and the reverted trend in BNO are highlighted graphically in Figure 1 and numerically in Figure 2.

Having cardiac disorder(s) was reported by 19.5% of the subjects of both genders and was a significant predictor only for ΔFEV_1 and ΔFVC, but it did not affect the estimates of the coefficient of the categories of obesity (i.e., it was not a confounding factor). Having diabetes was reported by 2.9% of the subjects of both genders and was neither a significant predictor of changes in lung function nor a confounding factor in any model considered.

Table 1 Baseline characteristics of study subjects by longitudinal category of obesity and gender.

	Males ($n = 590$)					Females ($n = 622$)				
	Never obese	Becoming obese	Always obese	Becoming non-obese	*P*	Never obese	Becoming obese	Always obese	Becoming non-obese	*P*
n	465	55	57	13		474	56	75	17	
Age (years)	41 (11)	44 (11)	45 (10)	48 (7)	0.0006	41 (11)	43 (10)	48 (10)	47 (10)	0.0000
Height (cm)	171 (7)	171 (7)	170 (7)	169(5)	0.3661	158 (5)	157 (7)	156 (5)	155 (5)	0.0001
Weight (kg)	73 (8)	81 (10)	93 (10)	88 (6)	0.0000	60 (8)	69 (7)	82 (10)	77 (7)	0.0000
BMI (kg/m^2)	25 (2)	28 (2)	32 (2)	31 (1)	0.0000	24 (3)	28 (2)	34 (3)	32 (2)	0.0000
FEV_1 (L)	3.6 (0.7)	3.5 (0.8)	3.3 (0.7)	3.0 (0.7)	0.0010	2.7 (0.4)	2.7 (0.5)	2.5 (0.4)	2.5 (0.3)	0.0000
FEV_1 (%pred)	95 (15)	94 (16)	94 (16)	89 (18)	0.5780	98 (12)	98 (13)	96 (11)	96 (11)	0.1057
FVC (L)	4.8 (0.8)	4.7 (0.9)	4.4 (0.8)	4.1 (0.6)	0.0003	3.5 (0.5)	3.5 (0.5)	3.2 (0.5)	3.0 (0.4)	0.0000
FVC (%pred)	98 (12)	98 (12)	98 (13)	92 (11)	0.2922	99 (12)	98 (12)	96 (10)	91 (11)	0.0004
VC (L)	4.9 (0.8)	4.9 (0.9)	4.6 (0.8)	4.2 (0.7)	0.0020	3.6 (0.5)	3.6 (0.5)	3.4 (0.5)	3.2 (0.4)	0.0000
VC (%pred)	98 (13)	97 (11)	96 (14)	89 (12)	0.0875	99 (12)	98 (13)	96 (11)	92 (10)	0.0038

Data presented are mean (SD). *P*-value across longitudinal categories of obesity by Kruskal–Wallis test.

Table 2 Mean absolute differences between values observed at follow-up and at baseline by longitudinal categories of obesity and gender.

	Males ($n = 590$)					Females ($n = 623$)				
	Never obese	Becoming obese	Always obese	Becoming non-obese	*P*	Never obese	Becoming obese	Always obese	Becoming non-obese	*P*
n	465	55	57	13		474	56	75	17	
Age (years)	8.2 (0.9)	8.3 (1.0)	8.1 (0.9)	8.3 (0.9)	0.5835	8.2 (0.9)	8.5 (1.0)	8.3 (0.9)	8.2 (0.6)	0.3108
Height (cm)	−1.0 (1.9)	−1.6 (2.1)	−0.9 (1.8)	−0.4 (1.7)	0.1047	−0.7 (2.0)	−1.4 (1.8)	−1.1 (1.9)	0.8 (1.9)	0.0003
Weight (kg)	1.7 (4.9)	9.2 (7.9)	2.7 (6.6)	−8.9 (9.8)	0.0000	2.0 (4.6)	8.8 (5.5)	1.1 (5.9)	−9.8 (8.8)	0.0000
BMI (kg/m^2)	0.9 (1.7)	3.7 (2.6)	1.3 (2.4)	−2.9 (3.2)	0.0000	1.0 (1.9)	4.1 (2.2)	0.9 (2.7)	−4.4 (3.4)	0.0000
ΔFEV_1 (L)	−0.17 (0.27)	−0.29 (0.23)	−0.16 (0.20)	−0.02 (0.31)	0.0007	−0.18 (0.19)	−0.30 (0.20)	−0.23 (0.19)	−0.16 (0.19)	0.0000
ΔFVC (L)	−0.13 (0.32)	−0.28 (0.31)	−0.21 (0.25)	0.04 (0.41)	0.0015	−0.14 (0.24)	−0.28 (0.27)	−0.26 (0.22)	−0.03 (0.35)	0.0000
ΔVC (L)	−0.10 (0.37)	−0.27 (0.30)	−0.18 (0.31)	0.02 (0.39)	0.0015	−0.09 (0.26)	−0.27 (0.28)	−0.28 (0.29)	−0.16 (0.21)	0.0000

Data presented are mean (SD). *P*-value across longitudinal categories of obesity by Kruskal–Wallis test.

Table 3 Estimated coefficients of the linear regression models for the variation of FEV_1 (ΔFEV_1), FVC (ΔFVC), and VC (ΔVC) in longitudinal categories of obesity, adjusted for sex, baseline age, and smoking habits.

	ΔFEV_1 (L)				ΔFVC (L)				ΔVC (L)			
	Coefficient	*P*	95% C.I.		Coefficient	*P*	95% C.I.		Coefficient	*P*	95% C.I.	
Becoming obese	−0.111	0.000	−0.157	−0.065	−0.122	0.000	−0.179	−0.066	−0.155	0.000	−0.216	−0.094
Always obese	−0.009	0.694	−0.052	0.034	−0.065	0.017	−0.118	−0.011	−0.109	0.000	−0.167	−0.051
Becoming non-obese	0.093	0.037	0.006	0.180	0.180	0.001	0.072	0.287	0.048	0.406	−0.066	0.162
Smoker	−0.050	0.002	−0.081	−0.019	−0.023	0.237	−0.062	0.015	−0.025	0.254	−0.068	0.017
Ex smoker	0.013	0.525	−0.028	0.055	−0.011	0.687	−0.062	0.041	−0.006	0.823	−0.063	0.050
Male sex	0.029	0.049	0.000	0.059	0.021	0.250	−0.015	0.057	0.015	0.466	−0.025	0.055
Age	−0.004	0.000	−0.005	−0.003	−0.007	0.000	−0.008	−0.005	−0.006	0.000	−0.007	−0.004
Constant	−0.001	0.975	−0.068	0.066	0.150	0.000	0.068	0.233	0.146	0.002	0.055	0.237

ΔFEV_1, ΔFVC, and ΔVC are computed as the FEV_1, FVC, and VC value (in L) measured at follow-up minus the value at baseline. 95% C.I. = 95% confidence intervals.

Discussion

The main findings of this study are that (1) obesity entails a faster but variable reduction of the spirometric parameters most representative for lung function decline and (2) loosing weight appears to be capable of diminishing the lung function decline linked to obesity. These findings may support the notion that obesity and lung function are tightly linked in a reversible but complex way.

Epidemiological evidences

Our findings are consistent with those from previous longitudinal studies, which demonstrated that weight gain affects lung function independently of age, smoking habit, and occupational exposure both in population-based[8,11,12] and occupational cohorts.[9,10] Thus, the relevant association between increasing weight and an accelerated decline in lung function is confirmed in this general population, where even small changes in adiposity affected lung function decline over an 8-year period of time.

We also observed that this trend may be reverted with weight loss. To our knowledge, no large longitudinal population-based study has specifically analyzed the effect of the reversibility of the obesity status on lung function decline. In a random sample of 9003 adults, Carey et al.[12] observed that subjects who lost weight between two surveys conducted 7 years apart did not on average gain lung function, but rather slowed down their rate of decline in

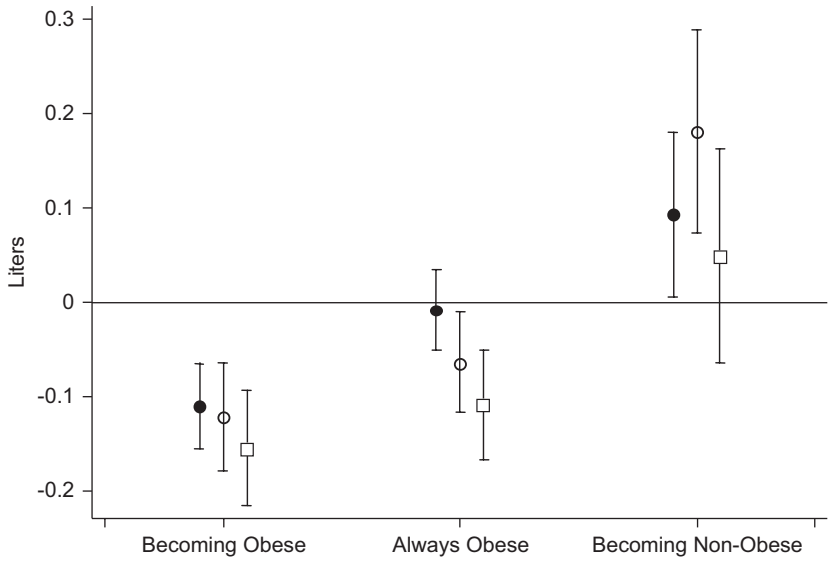

Figure 1 Mean variations (in liters) of ΔFEV_1, ΔFVC and ΔVC in three longitudinal categories of obesity with respect to the reference category of "never obese", based on the linear regression models reported in Table 3. Within each longitudinal category of obesity, the three bars refer to ΔFEV_1, (black circle), ΔFVC (open circle), and ΔVC (open square) from left to right, respectively.

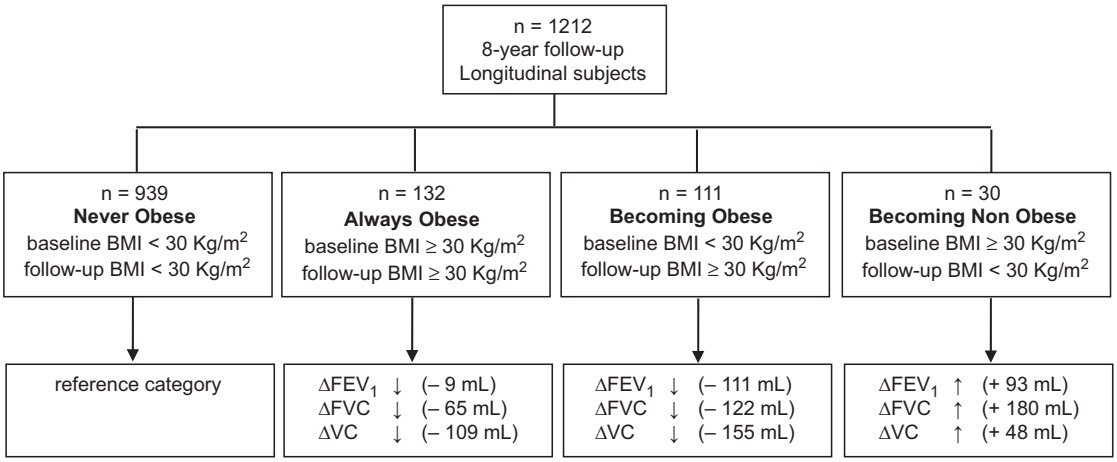

Figure 2 Study subjects by longitudinal categories of obesity and corresponding mean variations of $\Delta FEV1$, ΔFVC, and ΔVC (in milliliters) with respect to the reference category "Never obese", adjusted for baseline gender, age, and smoking habit in the linear regression models reported in Table 3.

comparison to others, even though no results on this analysis was reported. In a cohort of 181 workers followed-up for $\geqslant 6$ years, Morgan and Reger[18] showed that, regardless the smoking habit, the subjects who lost weight showed a smaller annual decrement in the FEV_1 than those who gained it (e.g., -0.029 vs. -0.039 L in non-smokers), even though the magnitude of weight change yielding such effect was not provided.

It is to point out that obesity is an important determinant of asthma, particularly for adults,[19] and overweight and obesity have been recently demonstrated to be associated with a dose-dependent increase in the probability of incident asthma in both genders.[20] Thus, the effect of changes in obesity status on lung function decline may have implications for public health, as weight-control programs might be also considered in relation to such a chronic airway disease.

Limitations of the study

BMI was taken as a surrogate of obesity, even though it is known that what counts to decrease lung volume in obesity is fat distribution (upper body vs. lower body)[21] and tissue composition (fat vs. lean mass).[22] Yet, BMI is a gross parameter largely used in epidemiological studies for its simplicity and practicability and gives us also the possibility to compare our findings with those reported in the literature.

We recognize that co-morbidities, such as diabetes and chronic heart failure, may affect lung function and its decline in obesity. However, according to the available information in our population, the rate of co-morbidities was similar across groups, thus suggesting that differences in decline were primarily caused by the obesity.

Lacking of a specific temporal question, our study does not allow to know when the changes in body weight occurred

during the 8-year period. In a future repetition of the study, it would be helpful to yearly monitoring the weight pattern in order to understand how long it takes for a variation in BMI to modify the lung function decline in real life.

We acknowledge the small range of BMI and its variations over time in our study. If on one side this prevents us from extrapolating our analysis to massive obesity, on the other hand it documents the importance of even small changes in BMI in impairing lung function over time.

Few subjects were included in the BNO category as compared with those included in the BO category, possibly limiting the power of the statistical analyses. However, this distribution among the longitudinal categories of obesity reflects the well-known trend in weight changes observed over time in the western countries.

Patho-physiological interpretation of the results

Obesity is known to cause a decrease in operational lung volume, thus gradually reducing the expiratory flow reserve within the tidal breathing range until flow limitation conditions and dyspnea occur, especially in the supine posture or with minimal physical activity.[7,23] Very recent studies have hypothesized that such a decrease of the operational lung volume may be one of the potential mechanisms explaining the observed link between obesity and bronchial asthma.[3]

In animal models, mechanical ventilation at low lung volume results in expiratory airflow limitation and inflammatory damage of the small airways, with denudation of the epithelium and sloughing and rupture of the alveolar attachments to the adventitia.[24,25] In a way, obesity is similar to ventilating small animals at low lung volume. The shear stress applied to the airways with the cyclic collapse on tidal expiration and the following opening on inspiration might lead to airway inflammation and repair/remodeling processes, and rupture of the alveolar attachments to the adventitia. However, considering the irreversible nature of such damages, this hypothesis partly contrasts with the reversible nature of lung function decline observed in this study with weight loss.

The reversibility of the accelerated decline in lung function with loosing weight speaks in favor of other factors that affect lung function decline as obesity persists. Firstly, obese individuals breathe with smaller tidal volume than controls and higher breathing frequency.[26] Breathing with low tidal volumes results in the conversion of rapidly cycling actin–myosin bridges to slow cycling latch bridges,[27] a condition expected to increase airway smooth muscle (ASM) tone and thus decrease airways size. Whether this mechanism contributes to explain our results is not known because of a concomitant increase in breathing frequency, which is capable of offsetting the increase in bronchial tone occurring when cyclic lengthening is reduced.[28] Secondly, the inability to expand the lung sufficiently to total lung capacity with large breaths[4,29] might gradually impair bronchial tone over time, thus contributing to exaggerate the observed lung function decline. Simulation of chest wall constraint with strapping has indeed shown that this may be the case.[30] Thirdly, the decline in lung function in obesity could be the result of a plastic adaptation of the ASM to a short length, as demonstrated by *in vitro* studies,[31] and suggested by the greater response to a constrictor agent observed in healthy humans after decreasing lung volumes.[30,32]

Interestingly, we noted that the decline in FEV_1 but not in FVC or VC in AO was significantly less than that of BO. We speculate that this could be due to the increase in lung elastic recoil reported in obesity.[33] Whereas the increased lung elasticity is expected to increase maximum flow and thus the FEV_1,[34] it has the opposite effect on vital capacity as the result of a decrease in total lung capacity greater than the decrease in residual volume.[4,29]

Conclusions

Over a period of 8 years, remaining or becoming obese accelerates lung function decline, while becoming non-obese decreases it. On the basis of existing evidences and present results, it appears advisable that lung function measurements be routinely performed during weight-control programs, to assess the effects of weight changes on respiratory health over time.

Conflict of interest statement

None of the authors have a conflict of interest to declare in relation to this work.

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References

1. Kopelman PG. Obesity as a medical problem. *Nature* 2000; **404**:635–43.
2. Lawrence VJ, Kopelman PG. Medical consequences of obesity. *Clin Dermatol* 2004;**22**(4):296–302.

3. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med* 2006;**174**:112–9.
4. Jones RL, Nzekwu M-MU. The effects of body mass index on lung volumes. *Chest* 2006;**130**:827–33.
5. King GG, Brown NJ, Diba C, et al. The effects of body weight on airway calibre. *Eur Respir J* 2005;**25**:896–901.
6. Partridge MR, Ciofetta G, Hughes JMB. Topography of ventilation–perfusion ratios in obesity. *Bull Eur Physiopathol Respir* 1978;**13**:765–73.
7. Ferretti A, Giampiccolo P, Cavalli A, et al. Expiratory flow limitation and orthopnea in massively obese subjects. *Chest* 2001;**119**:1401–8.
8. Bottai M, Pistelli F, Di Pede F, et al. Longitudinal changes of body mass index, spirometry and diffusion in a general population. *Eur Respir J* 2002;**20**:665–73.
9. Wang ML, McCabe L, Petsonk EL, et al. Weight gain and longitudinal changes in lung function in steel workers. *Chest* 1997;**111**:1526–32.
10. Chinn DJ, Cotes JE, Reed JW. Longitudinal effects of change in body mass on measurements of ventilatory capacity. *Thorax* 1996;**51**:674–99.
11. Chen Y, Horne SL, Dosman JA. Body weight and weight gain related to pulmonary function decline in adults: a six year follow up study. *Thorax* 1993;**48**:375–80.
12. Carey IM, Cook DG, Strachan DP. The effects of adiposity and weight change on forced expiratory volume decline in a longitudinal study in adults. *Int J Obes Relat Metab Disord* 1999;**23**:979–85.
13. Paoletti P, Pistelli G, Fazzi P, et al. Reference values for vital capacity and flow–volume curves from a general population study. *Bull Eur Physiopathol Respir* 1986;**22**:451–9.
14. Pistelli F, Bottai M, Viegi G, et al. Smooth reference equations for slow vital capacity and flow–volume curve indexes. *Am J Respir Crit Care Med* 2000;**161**:899–905.
15. Viegi G, Paoletti P, Prediletto R, et al. Prevalence of respiratory symptoms in an unpolluted area of northern Italy. *Eur Respir J* 1988;**1**:311–8.
16. Ferris BG. Epidemiology standardization project. *Am Rev Respir Dis* 1978;**118**(6, Part 2):255–88.
17. Pistelli G, Carmignani G, Paoletti P, et al. Comparison of algorithms for determining the end-point of the forced vital capacity maneuver. *Chest* 1987;**91**:100–5.
18. Morgan WKC, Reger RB. Rise and fall of the FEV_1. *Chest* 2000; **118**:1639–44.
19. Camargo Jr CA, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999; **159**(21):2582–8.
20. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;**175**(7):661–6.
21. Lazarus R, Sparrow D, Weiss ST. Effects of obesity and fat distribution on ventilatory function. The Normative Aging Study. *Chest* 1997;**111**:891–8.
22. Willett W. Anthropometric measures and body composition. 1st ed. MacMahon B, editor. *Nutritional epidemiology, monograph in epidemiology and biostatistics*, 15. New York: Oxford University Press; 1999.
23. Muscedere JG, Mullen JBM, Gan K, et al. Tidal ventilation at low airway pressure can augment lung injury. *Am J Respir Crit Care Med* 1994;**149**:1327–34.
24. D'Angelo ED, Pecchiari M, Boraggia P, et al. Low-volume ventilation causes peripheral airway injury and increased airway resistance in normal rabbits. *J Appl Physiol* 2002; **92**:949–56.
25. Pankow W, Podszus T, Gutheil T, et al. Expiratory flow limitation and intrinsic positive end-expiratory pressure in obesity. *J Appl Physiol* 1998;**85**:1236–43.
26. Sampson MG, Grassino AE. Load compensation in obese patients during quiet tidal breathing. *J Appl Physiol* 1983;**55**: 1269–76.
27. Fredberg JJ, Jones KA, Nathan M, et al. Friction in airway smooth muscle: mechanism, latch, and implications in asthma. *J Appl Physiol* 1996;**81**:2703–12.
28. Shen X, Gunst SJ, Tepper RS. Effect of tidal volume and frequency on airways responsiveness in mechanically ventilated rabbits. *J Appl Physiol* 1997;**83**:1202–8.
29. Collins LC, Hoberty PD, Walker JF, et al. The effect of body fat distribution on pulmonary function tests. *Chest* 1995;**107**: 1298–302.
30. Torchio R, Gulotta C, Ciacco C, et al. Effects of chest wall strapping on mechanical response to methacholine in humans. *J Appl Physiol* 2006;**101**:430–8.
31. Gunst SJ, Meiss RA, Wu MF, et al. Mechanisms for the mechanical plasticity of tracheal smooth muscle. *Am J Physiol* 1995;**268**:C1267–76.
32. Meinero M, Coletta G, Dutto L, et al. Mechanical response to methacholine and deep breath in supine posture in men. *J Appl Physiol* 2007;**102**:269–75.
33. Pelosi P, Croci M, Ravagnan I, et al. Respiratory system mechanics in sedated, paralyzed, morbidly obese patients. *J Appl Physiol* 1997;**82**:811–8.
34. Hyatt RE. Forced expiration. The respiratory system. Mechanics of breathing. In: Macklem PT, Mead J, editors. *Handbook of physiology.* Bethesda: American Physiological Society; 1986. p. 295–314.